REMARKS

Claims 33-59 were pending. Claims 41-44 have been amended.

Specifically, claims 41-44 have been amended to remove "conservative sequence modifications." Support for this amendment can be found throughout the application as originally filed.

The foregoing claim amendments should in no way be construed as acquiescence to any of the Examiner's rejections and were made solely to expedite prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s). No new matter has been added.

Rejection of Claims 41-44 Under 35 U.S.C. §112, First Paragraph

Claims 41-44 are rejected as not being enabled. Specifically, the Examiner states that the specification "does not reasonably provide enablement for any antibody comprising 'conservative modifications thereof' or 'substantially homologous to' the SEQ ID NOs disclosed in claims 41-44."

Applicants respectfully traverse this rejection for the reasons previously of record. Notwithstanding, to expedite prosecution, claims 41-44 have been amended to remove the subject matter rejected by the Examiner. Accordingly, this rejection should be moot.

Rejection of Claims 41-44 Under 35 U.S.C. §112, First Paragraph

Claims 41-44 are rejected as failing to comply with the written description requirement. The Examiner states that Applicants are "not in possession of any antibody comprising 'conservative modifications thereof' or 'substantially homologous to' the SEQ ID NOs disclosed in claims 41-44."

Applicants respectfully traverse this rejection for the reasons previously of record. Notwithstanding, to expedite prosecution, claims 41-44 have been amended to remove the subject matter rejected by the Examiner. Accordingly, this rejection should be moot.

Rejection of Claims 33-37, 39-45, and 47-59 Under 35 U.S.C. §102(b)

Claims 33-37, 39-45, and 47-59 are rejected as being anticipated by WO 01/85798. Specifically, the Examiner asserts that the '798 publication teaches

> [t]he identical immune conjugate [as claimed] comprising an antigen and a monoclonal antibody that binds to human mannose receptor via the identical method of contacting (*e.g.*, *in vivo* and *ex vivo* internalization of antigen by APC), the mechanism of inducing the cytotoxic T cell response by both MHC Class I and Class II pathways or CD4+ and CD8+ are an inherent property of the immune conjugate comprising an antigen and a monoclonal antibody that binds to human mannose receptor.

Applicants respectfully disagree that WO 01/85798 inherently anticipates the claimed invention. The present claims are directed to methods for inducing a cytotoxic T cell (CTL) response against an antigen mediated by both $CD4^+$ and $CD8^+$ T cells. Inherency is established if "the natural result flowing from the operation as taught would result in the performance of the questioned function . . . ." *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1269 (Fed. Cir. 1991). However, "[i]nherency may not be established by probabilities or possibilities." *Scaltech, Inc. v. Retec/Tetra, LLC.*, 178 F.3d 1378, 1384 (Fed. Cir. 1999). To establish a case of inherent anticipation, the claimed method must have existed or occurred to a certainty. *Scaltech, Inc. v. Retec/Tetra, LLC.*, 269 F.3d 1321, 1330 (Fed. Cir. 2001).

Accordingly, in the present case, because of the proven unpredictability of generating the claimed CTL response mediated by both MHC Class I and Class II pathways using an antigen-antibody conjugate targeted to the human MMR (as discussed in detail below), the cited reference fails to anticipate the claimed methods. Indeed, Applicants were the first to demonstrate that the generation of such a CTL response, mediated by both MHC Class I and Class II pathways, was possible by using an antibody targeted to the human MMR. The prior art including the cited reference, WO 01/85798, fails to exemplify the claimed methods or show that it was predictable or even possible to induce such a CTL response as claimed, let alone show that the claimed method "existed or occurred to a certainty."

Specifically, at the time the present application was filed, the prior art (including the cited reference, WO 01/85798) had not shown that CTL responses mediated by both MHC Class I and Class II pathways could be achieved, as currently claimed. In fact, immune responses shown in the prior art were limited to those mediated by MHC Class II presentation to CD4 helper T cells. Helper T cells, in general, do not have any direct cytotoxic activity and, thus, achieving enhanced CD4 responses (*i.e.*, MHC Class II) alone would not have provided motivation to one of ordinary skill in the art to have tried developing a therapeutic immunization strategy, *e.g.*, for cancers or other disorders. This is true in particular for intracellular antigens (see, *e.g.*, claim 46), such as Pmel-17, for which a cytolytic T cell response (as taught by Tuting *et al.* (1998); enclosed as Appendix A) is critical for the cytolytic effect. In order to generate

CTL responses that are mediated by both pathways, the antigen must be presented by the antigen presenting cell on MHC Class I molecules, which the prior art had not shown. Moreover, the intracellular pathways for MHC Class II and Class I presentation are completely distinct, and one can not extrapolate from the data of the prior art which pertains to enhancement of MHC Class II presentation, that targeting to the mannose receptor would also enhance MHC Class I presentation, and thereby CTL responses. Thus, the prior art (including the cited reference, WO 01/85798) would not have motivated one of ordinary skill in the art to have used an antibody against human MMR to elicit a CTL response mediated by both MHC Class I and Class II pathways, as currently claimed.

Moreover, even if the claimed CTL response mediated by both MHC Class I and Class II pathways using an antigen-antibody conjugate targeted to the human MMR would have been produced by the cited reference, WO 01/85798, such results would have occurred at best "occasionally" in light of the proven unpredictability of generating the claimed CTL response (as described in detail above). As held by the Federal Circuit, "[o]ccasional results are not inherent." *MEHL/Biophile Int'l Corp. v. Milgraum*, 192 F.3d 1363, 1364 (Fed. Cir. 1999).

Accordingly, based at least on the foregoing, the cited reference fails to anticipate the claimed invention.

Rejection of Claims 33, 38 and 46 Under 35 U.S.C. §103(a)

Claims 33, 38 and 46 are rejected as being unpatentable over WO 01/85798 in view of US 5,869,057. The Examiner admits that WO 01/85798 "does not teach the use of βhCG as an antigen." However, the Examiner relies on US 5,869,057 as teaching "the use of βhCG as an antigen . . . as well as its capacity to present antigen to CD4+ cells."

Applicants respectfully traverse this rejection. As discussed above (the substance of which is reiterated here), the primary reference (WO 01/85798) does not anticipate the presently claimed methods given the lack of certainty in the art for generating the claimed CTL response mediated by both MHC Class I and Class II pathways using an antigen-antibody conjugate targeted to the human MMR.

The secondary reference, the '057 patent, fails to make up for this deficiency. Specifically, the '057 patent fails to teach the claimed methods or provide any guidance for predictably generating the claimed CTL response. In fact, the '057 fails to teach of suggest using any type of antibody and states that its invention provides advantages over the prior art (which includes the use of antibody technology). In particular, the '057 patent teaches linking

(via recombinant DNA technology) a microbial (non-self) gene product (*e.g.*, a prokaryotic helper T cell epitope, such as heat-labile entertoxin B subunit (LTB)) to a "self" gene product (*e.g.*, a βhCG epitope) for the production of an immune response to the self protein. The '057 patent fails to teach or suggest using any type of antibody and states that its invention provides advantages over the prior art (which includes the use of antibody technology). For example, the '057 patent states (at col. 11, ll. 63(that:

> [the] invention offers four primary advantages over prior art. First, recombinant DNA technology enables consistent production of a defined vaccine formulation. This is superior to peptide synthesis and chemical conjugation, which lead inevitably to variability in preparation that can affect vaccine potency. Second, due to the natural action of microbial products, my invention precludes the need for additional adjuvants such as muramyl dipeptide in the final vaccine formulation. Third, recombinant protein expression enables lower costs of vaccine manufacture relative to the significant expense of peptide synthesis and chemical conjugation. Finally, recombinant expression of self proteins in a form linked to microbial products may facilitate the introduction of such formulations via mucosal immunization. This could feasibly include oral, nasal, or rectal administration and is not possible with the chemical conjugates described above.

Based at least on the foregoing, the claims are patentable over the cited references.

Rejection of Claim 33-59Under 35 U.S.C. §112, First Paragraph

Claims 33-59 are rejected as encompassing new matter. Specifically, the Examiner states that "[t]he specification as filed does not provide a written description for the phrase "human **macrophage** mannose receptor" [emphasis in original].

Applicants respectfully traverse this rejection. The specification explicitly teaches, for example, at page 10, lines 13-22, that:

> [i]n a particular embodiment, the antibody is a human monoclonal antibody that binds to the **human macrophage mannose receptor** (also referred to herein as "human B11 antigen") having an approximate molecular weight of 180 kD as measured by SDS-PAGE. Protocols for generating such antibodies are described in WO 01/085798, the contents of which are incorporated herein by reference. Particular human antibodies include those which comprise heavy and light chain variable regions amino acid sequences as shown in SEQ ID NOs: 2 and 6, respectively, or an amino acid sequence that is sufficiently homologous to SEQ ID NO:2 or SEQ ID NO:6 such that the antibody retains the ability to bind to dendritic cells [emphasis added].

Accordingly, claims 33-59 are fully supported by the present specification and do not encompass new matter.

SUMMARY

Based on the foregoing amendments and arguments, reconsideration and withdrawal of all the rejections and allowance of this application with all pending claims are respectfully requested. If a telephone conversation with Applicants' Attorney would expedite the prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7400.

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Respectfully submitted,

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